Case No. 1:23-cv-629

Natera, Inc. v. NeoGenomics Laboratories, Inc.

CLAIM CONSTRUCTION HEARING

NeoGenomics' Demonstratives

March 11, 2025

NEO GENOMICS

Term A: "the isolated cell-free DNA"

NeoGenomics' Proposal	Natera's Proposal
Plain and ordinary meaning, which ***is*** cell-free DNA isolated from ***a plurality*** of biological samples obtained from the subject	Plain and ordinary meaning, which ***includes*** cell-free DNA isolated from ***any of the plurality*** of biological samples obtained from the subject ***at different time points***.

Joint Claim Construction Chart, ECF No. 370-1 at 1

Natera *Rewrites* NeoGenomics' Proposed Construction

A. "the isolated cell-free DNA"

Natera's Proposal:	**NeoGenomics' Proposal[5]:**
Plain and ordinary meaning, which includes cell-free DNA isolated from any of the plurality of biological samples obtained from the subject at different time points.	Plain and ordinary meaning, which is cell-free DNA isolated from a plurality of biological samples obtained from the subject and excludes cell-free DNA isolated from a single biological sample obtained from the subject.

Natera Opening Brief, ECF No. 372 at 8

Neo's Construction Tracks the Claim Language

(c) assaying cell-free DNA isolated from a plurality of biological samples obtained from the subject at different time points, wherein the assaying comprises:

performing targeted multiplex PCR amplification to amplify the plurality of target loci together in the same reaction volume from the isolated cell-free DNA using primers specific to the plurality of target loci for the individual subject; and

'596 Patent at 172:1-9

NeoGenomics' Proposal

Plain and ordinary meaning, which is cell-free DNA isolated from a plurality of biological samples obtained from the subject

Natera's Construction Rewrites "a plurality" to "any of the plurality"

any of the

(c) assaying cell-free DNA isolated from ~~a~~ plurality of biological samples obtained from the subject at different time points, wherein the assaying comprises:

performing targeted multiplex PCR amplification to amplify the plurality of target loci together in the same reaction volume from the isolated cell-free DNA using primers specific to the plurality of target loci for the individual subject; and

'596 Patent at 172:1-9

Natera's Proposal

Plain and ordinary meaning, which ***includes*** cell-free DNA isolated from ***any of the*** plurality of biological samples obtained from the subject at different time points.

“The” Must Have an Antecedent Basis

Eastman Chem. Co. v. Aktiengesellschaft, 47 F. App'x 566, 573 (Fed. Cir. 2002)

construing “the salt” to refer to the product of prior step because “[a] plain reading of the claims shows that the term refers to the salt earlier described” and “the word ‘the’ must have an antecedent basis”

"The" Must Refer to the Earlier Term in the Claim, Not Some Other Selection or Subset

Guardant Health, Inc. v. Found. Med. Inc., No. CV 17-1616-LPS-CJB, 2019 WL 5677748, *10 (D. Del. Nov. 1, 2019)

"The Court therefore agrees with Defendants that (absent some other strong indication to the contrary) 'the plain language [of these claims] requires grouping *the same* set of sequence reads referred to in the prior step—not some other selection or subset of sequence reads.' . . . After all, the claims do not say "grouping any of the plurality of sequence reads" or "grouping some of the plurality of sequence reads"—rather, they require grouping of "the" sequence reads referred to in the prior step."

"The" Must Refer to the Earlier Term in the Claim, Not Some Other Selection or Subset

Harris Corp. v. Fed. Exp. Corp., 502 F. App'x 957, 963–64 (Fed. Cir. 2013)

"Given this claim's prior description of . . . a particular set of data in the ground data link unit, it is entirely reasonable to interpret "transmitting the accumulated, stored generated aircraft data from the ground data link unit" as referring to that same data set. This is especially true where, as here, the later instance refers to "the" data and therefore begs for some antecedent basis. . . . [A]lthough the claim does not expressly require that 'all' of the accumulated data must be transmitted, it similarly lacks any indication that some subset of the accumulated data should be transmitted, and if so what that subset should be. . . . [W]e [adopt] FedEx's proposed construction: 'transmitting all the aircraft data that has been accumulated or stored or generated.'"

The Court Cannot Rewrite Unambiguous Patent Claim Language

Chef Am., Inc. v. Lamb-Weston, Inc., 358 F.3d 1371, 1375 (Fed. Cir. 2004)

"[T]he patentees had two models before them: the heating "to" limitation of the specification and original Claim 6 or the heating "at" limitation of the example. They chose the "to" limitation which, as we have shown, plainly and unequivocally refers to the temperature to which the dough and not the air in the oven will be heated. . . . Chef America does not contend that the patentees' use of 'to' rather than 'at' was a draftsman's mistake. . . . To the contrary they argue only that 'to' should be construed to mean 'at' because otherwise the patented process could not perform the function the patentees intended. As we have noted, however, we have repeatedly declined to rewrite unambiguous patent claim language for that reason."

Claim 17 does not change Claim 1

1. A method for preparing biological samples useful for monitoring the progression of cancer in a subject, the method comprising:

(a) performing sequencing on a tumor biopsy sample of the subject to identify a plurality of tumor-specific mutations, wherein the tumor-specific mutations comprise one or more single nucleotide variant (SNV) mutations;

(b) evaluating results of the sequencing on the tumor biopsy sample to determine a plurality of target loci specific to the subject, wherein each target locus spans a tumor-specific mutation of the identified plurality of tumor-specific mutations; and

(c) assaying cell-free DNA isolated from a plurality of biological samples obtained from the subject at different time points, wherein the assaying comprises:

performing targeted multiplex PCR amplification to amplify the plurality of target loci together in the same reaction volume from the isolated cell-free DNA using primers specific to the plurality of target loci for the individual subject; and

performing high-throughput sequencing of the amplified DNA comprising the plurality of target loci to obtain sequence reads, wherein an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA having the SNV locus is detected from the sequence reads.

'596 Patent at Claim 1

17. The method of claim **1**, wherein the biological sample is a blood, serum, plasma, or urine sample.

'596 Patent at Claim 17

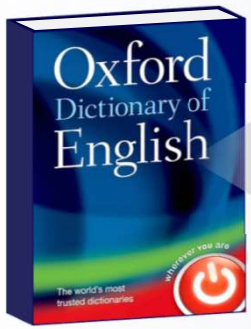
Term D: "wherein an SNV mutation . . . is detected from the sequence reads"

"performing high-throughput sequencing of the amplified DNA comprising the plurality of target loci to obtain sequence reads, wherein an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA having the SNV locus is detected from the sequence reads"

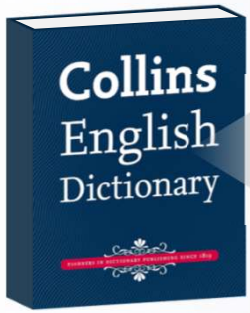
NeoGenomics' Proposal	Natera's Proposal
Plain and ordinary meaning, which is wherein an SNV mutation is determined to be present from the sequence reads	Plain and ordinary meaning, which means that the terms are part of the "performing high-throughput sequencing . . . to obtain sequence reads" step and the "wherein" clause informs the mechanics of how the high-throughput sequencing is performed.

Joint Claim Construction Chart, ECF No. 370-1 at 11

Natera's Dictionary Definitions Of "Detect" Support Neo's Proposed Construction



"to discover or identify the presence or existence of . . ."



"to discover the existence or presence of . . ."

Dkt. 372, 15-16

Dr. Metzker Could Not Explain the Difference between Detecting An SNV and Determining the SNV Is Present

Q. Okay. So what needs to happen in your view to go from detecting the SNV to determining the SNV is present?

A. I have no idea. I haven't considered what needs to be done to go from one term to another. I just think the construction is wrong.

Metzker Deposition at 44:22-45:11

Dr. Metzker Proposes a Non-Standard Meaning

Q. Now, the way that you understand the use of the term detect in the context of the patent, is that the same as how you understand persons of skill in the art used the term detect in the context of sequencing generally?

A. No.

Metzker Deposition at 106:18-23

The Specification Equates "Detecting" with "Determining"

In certain aspects, provided herein are methods for detecting single nucleotide variants in a sample. Accordingly, provided herein is a method for determining whether a single nucleotide variant is present at a set of genomic positions in a sample from an individual, the method comprising:

'596 Patent at 5:4-9

The Specification Equates "Detecting" with "Determining"

Exemplary Embodiments for Detecting Single Nucleotide Variants

In certain aspects, provided herein are methods for detecting single nucleotide variants in a sample. The improved methods provided herein can achieve limits of detection of 0.015, 0.017, 0.02, 0.05, 0.1, 0.2, 0.3, 0.4 or 0.5 percent SNV in a sample. All the embodiments for detecting SNVs can be carried out with a system. The disclosure provides teachings regarding specific functional and structural features to carry out the methods. Furthermore, provided herein are embodiments comprising a nontransitory computer readable medium comprising computer readable code that, when executed by a processing device, causes the processing device to carry out the methods for detecting SNVs provided herein.

'596 Patent at 65:14-29

Accordingly, provided herein in one embodiment, is a method for determining whether a single nucleotide variant is present at a set of genomic positions in a sample from an individual, the method comprising:

a. for each genomic position, generating an estimate of efficiency and a per cycle error rate for an amplicon spanning that genomic position, using a training data set;
b. receiving observed nucleotide identity information for each genomic position in the sample;
c. determining a set of probabilities of single nucleotide variant percentage resulting from one or more real mutations at each genomic position, by comparing the observed nucleotide identity information at each genomic position to a model of different variant percentages using the estimated amplification efficiency and the per cycle error rate for each genomic position independently; and
d. determining the most-likely real variant percentage and confidence from the set of probabilities for each genomic position.

'596 Patent at 65:30-51

In illustrative embodiments of the method for determining whether a single nucleotide variant is present, the estimate of efficiency and the per cycle error rate is generated for a set of amplicons that span the genomic position. For example, 2, 3, 4, 5, 10, 15, 20, 25, 50, 100 or more amplicons can be included that span the genomic position.

In illustrative embodiments of the method for determining whether a single nucleotide variant is present, the observed nucleotide identity information comprises an observed number of total reads for each genomic position and an observed number of variant allele reads for each genomic position.

In illustrative embodiments of the method for determining whether a single nucleotide variant is present, the sample is a plasma sample and the single nucleotide variant is present in circulating tumor DNA of the sample.

'596 Patent at 65:52-67

Dr. Metzker Also Uses "Detecting" and "Determining" Interchangeably

Q. Okay. So what, if any, are the mechanics of the claim that are required as a function of the wherein clause?

A. Well, the mechanics are performing some kind of sequencing process where base calls are being made . . . the mechanics are going through that process of being able to identify the base at that location, and the ability to either determine or to detect the presence or the absence of the SNV mutation.

Metzker Deposition at 32:11-24

Q. What do you understand the word from to mean in the context of the claim?

A. Well, I think the way I've described it as the mechanics of the sequencing where you're performing base by base, and that will start building the sequence read, that as that sequence read is being built at that position, if you know the SNV mutation exists based on the fluorescent signal, determining or detecting whether the SNV mutation is present or not.

Metzker Deposition at 37:23-38:6

Dr. Metzker Also Uses "Detecting" and "Determining" Interchangeably

Q. Sure. So you go through all these steps. You know the position of the interest. You get the readout of the sequencer. You know it should be a T. The readout of the sequencer tells you it's a T. You've detected, according to you, the rare genetic DNA variant, right?

* * *

A. I think I've explained this many times. Based on the fluorescence intensity . . . at that cycle, based on the way multiplex – targeted multiplex PCR assay has been designed, you will measure the fluorescence intensity and determine whether it's present or absent.

Metzker Deposition at 98:1-16

Dr. Metzker Says Making a Base Call Is Different From Determining The SNV Is Present

Q. So if I see the fluorescent signal, the machine sees the fluorescent signal and it makes the base call, has it determined whether an SNV is present?

A. No, I don't think it has.

Metzker Deposition at 44:22-45:11

Dr. Metzker Says Making a Base Call Is Determining the SNV Is Present

Q. And so is it your position that that base call then is sufficient to determine whether an SNV mutation is present?

A. It is, based on the way the claim is constructed, yes.

Metzker Deposition at 63:14-18

Natera's Evidence Describes Detection of Bases, Not SNV Mutations

for an Illumina high-throughput sequencing instrument, called HiSeq 2500. *Id.* at p. 24 (citing Ex. 2). The product sheet explains the operations occurring *within* the sequencing platform, stating:

> With the HiSeq 2500 System, high data quality is ensured by leveraging the most widely adopted chemistry in the industry: sequencing by synthesis (SBS). SBS technology on the HiSeq 2500 utilizes a proprietary reversible terminator-based method that ***detects single bases as they are incorporated into DNA template strands***.

Id. at 1 (emphasis added). In the context of sequencing at the time of the April 2015 priority date, a POSA would understand that the plain and ordinary meaning of the claimed "detected" limitation refers back to and modifies how the high-throughput sequencing is performed and that the detecting is part of the high-throughput sequencing happening in the sequencer. *See* Doc. 272 (Natera's '454 Patent Responsive Claim Construction Brief) at 16-17.

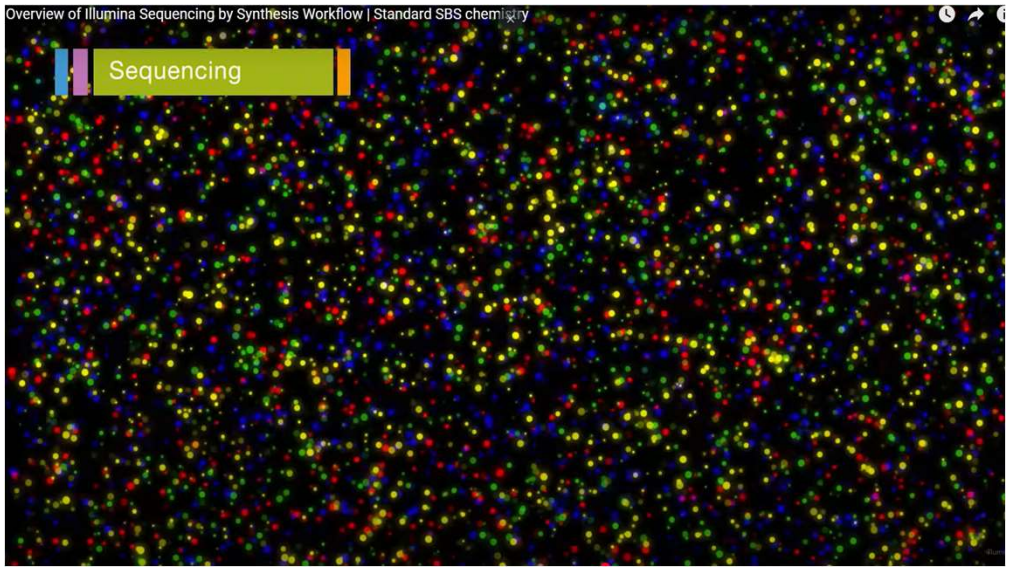
Natera Opening Brief, Dkt. 372 at 15

Dr. Metzker: Color is Enough to Identify an SNV

Q. Sure. You said that color is enough to identify a base. Is color enough to identify an SNV?

A. Yes. And because a base at a given location is either going to be represented by the normal base or the SNV mutated base.

Metzker Deposition at 16:3-7



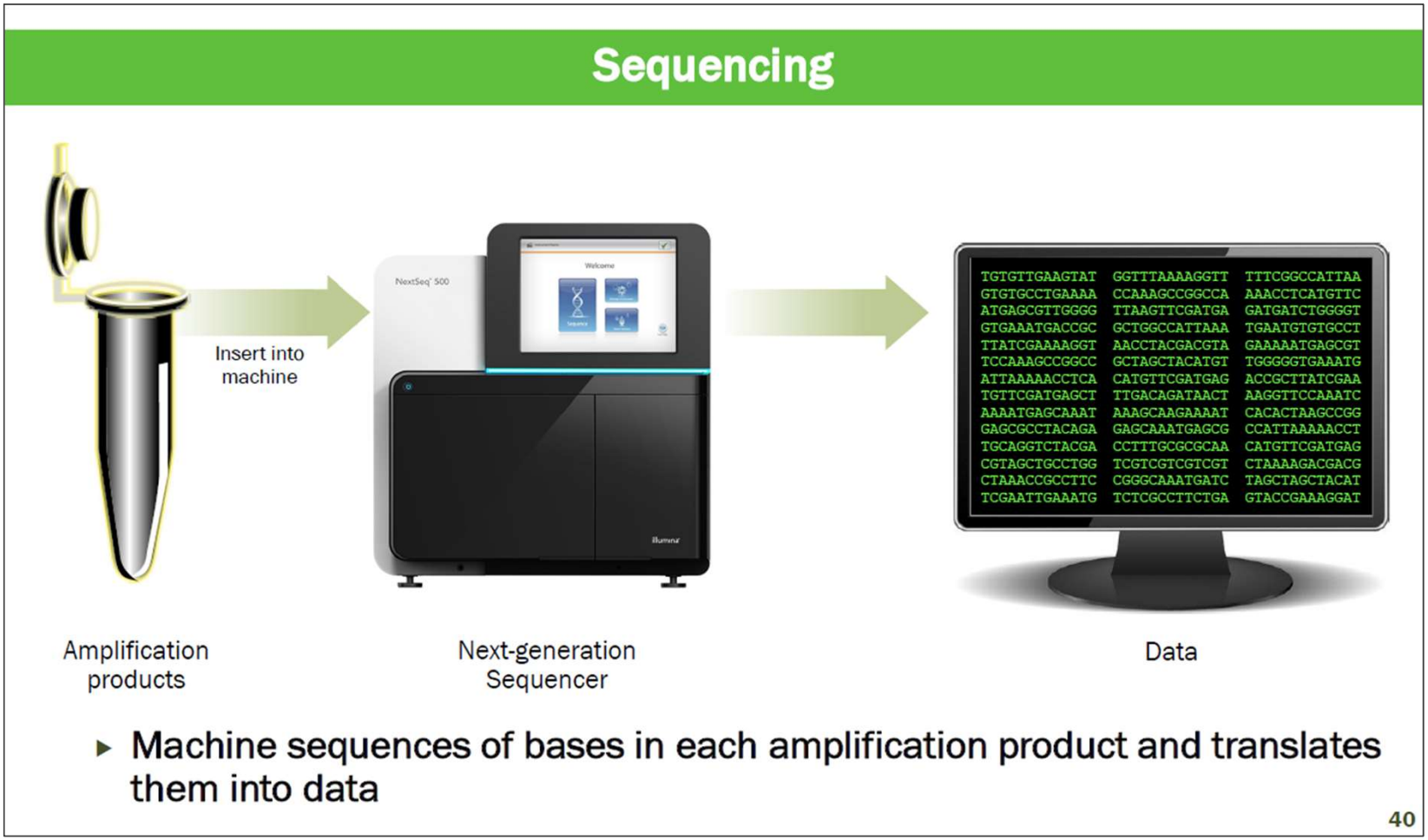
Overview of Illumina Sequencing by Synthesis Workflow | Standard SBS chemistry, https://www.youtube.com/watch?v=fCd6B5HRaZ8

The Claim Requires SNV Detection "from the sequence reads"

performing high-throughput sequencing of the amplified DNA comprising the plurality of target loci to obtain sequence reads, wherein an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA having the SNV locus is detected from the sequence reads.

'596 Patent at 172:9-14

Dr. Metzker's PI Tutorial: Sequencing Generates Sequence Reads



Natera Technology Tutorial at Preliminary Injunction at 40 (Nov. 9, 2023)

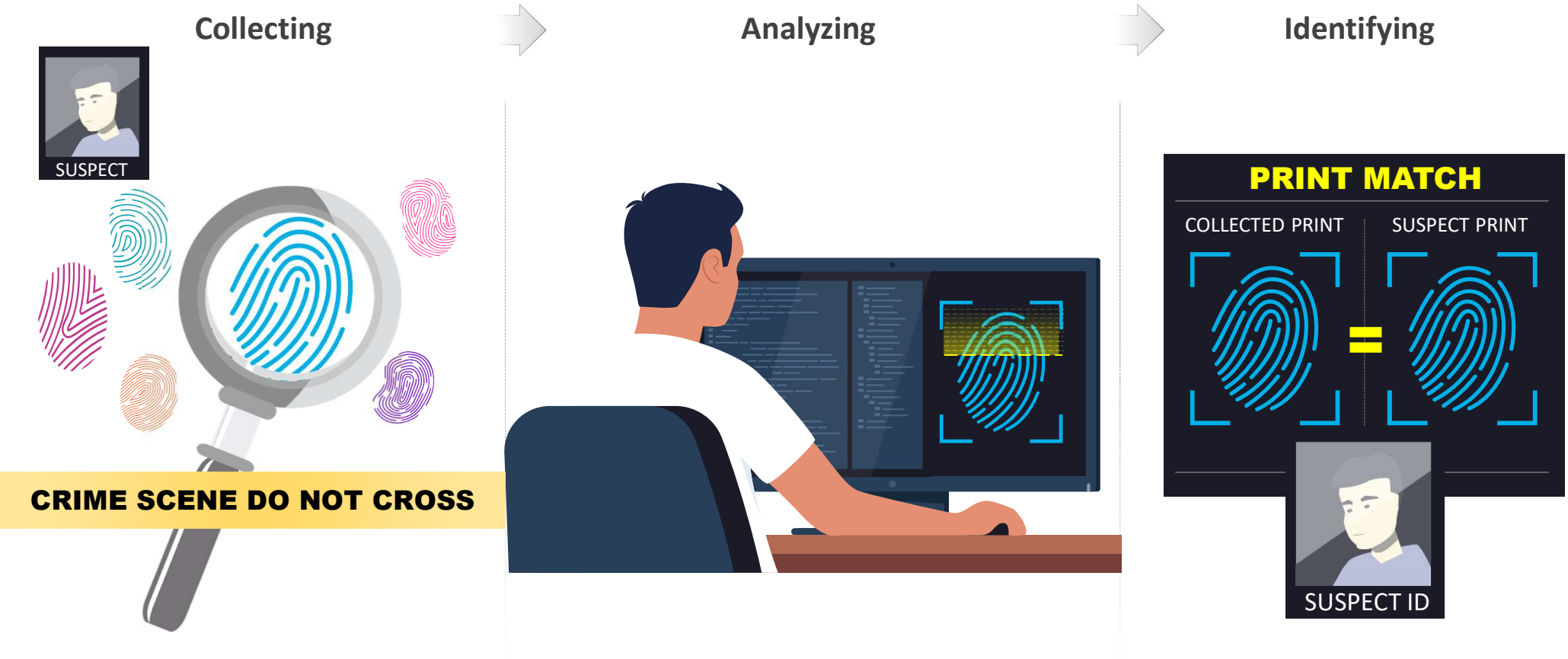
Dr. Metzker PI Deposition: Analysis is Required to Detect an SNV

Q. I -- I was asking about how the variants that are in the sequencing data from the cell-free DNA are identified. Do you know how that's done?

A. Well, my understanding, based on the public documents, is they used high throughput sequencing to generate sequence reads, and then there's a bioinformatic pipeline to identify whether the variants that are in the assays are detected or not.

Metzker 9/26/2023 Deposition during PI at 62:25-63:7

A Base Call Does Not Itself Detect an SNV Mutation



Dr. Metzker Said the Same in the *Guardant* Trial

Q. …. [C]ould you just explain what we're depicting here and how it relates to your opinions?

* * *

A. The sequencing step then actually decodes the genetic material into information, which is shown as the bioinformatics pipeline. And now we just have letters, our As, Cs, Gs, and Ts, but this is where we can then analyze whether mutations are present that we are looking for to either make a determination whether a circulating-tumor DNA is present or not.

Guardant Health, Inc. v. Natera, Inc., Trial Testimony of Dr. Metzker (12/15/2024) at 1683:18-20, 1684:10-15 (NEOGEN00290537)

Natera's CEO Dr. Rabinowitz Agreed

Q. How does Signatera tell you whether a patient's cancer is recurring?

A. We target the 16 variants in the blood. And we then take a blood draw from the patient, and we perform this test where we amplify up the DNA. We then sequence the DNA, and we then apply a bunch of signal processing or informatics algorithms to look for the presence of those variants that are unique to that patient's cancer.

Guardant Health, Inc. v. Natera, Inc., Trial Testimony of Dr. Rabinowitz (12/14/2024) at 1397:1-8 (NEOGEN00290249)

Natera's CEO Dr. Rabinowitz Agreed

Q. And can you just generally provide a high-level description of how Signatera works?

* * *

A. And we extract the DNA from the blood sample. We amplify it up with these very particular positions, we then sequence what we amplify. And then we run it through a bunch of signal-processing algorithms to boost up the signal, reduce the noise, and see whether those mutations are present in the blood.

Guardant Health, Inc. v. Natera, Inc., Trial Testimony of Dr. Rabinowitz (12/14/2024) at 1402:15-16, 1403:3-8 (NEOGEN00290255)

Dr. Metzker Equates Detecting With Whether the Mutation Is Present

Q. And in that example, the – in your view of the world, the NSV is detected at the point in time that the case is called, is that fair?

A. Well, it's not necessarily my point of the world, but given my background and experience and understanding of how sequencing technology works, and the way that the assaying cell-free DNA is performed using target specific primers looking for known SNV mutations, you will know which cycle the SNV mutation appears, and the fluorescent color based on which nucleotide is incorporated will tell you whether the SNV mutation is present or absent.

Metzker Deposition at 11:18-12:3

Natera's Construction Would Mean Detection of an Error is "Detection" of an SNV Mutation

Q. Now, it is your position that even if such errors take place, you are still detecting an SNV if you see the signal that corresponds to an SNV at the correct location, even if that signal turns out to be an error, right?

A. In the sequencing process, when fluorescence is being detected, the base call is making the base call based on the nucleotide that's being incorporated.

Metzker Deposition at 88:5-12

Detection of mutations in patient requires downstream analysis

Q. At the point in time when you call the base, and the base is the same as the expected mutation, at that point in time, is it your testimony that you have detected an SNV mutation in the patient?

A. I have not provided that opinion. That's not my testimony. It would be detecting an SNV mutation in the sequence read.

Q. Right. But I'm just asking you, as people like you of skill in the art in the field use the word detect, would you say that you have detected an SNV mutation in the patient?

A. I would think you would do a lot more downstream analysis to actually make the determination.

Metzker Deposition at 135:7-29

The Detected SNV Mutation Must be Present in the Cell-Free DNA

performing high-throughput sequencing of the amplified DNA comprising the plurality of target loci to obtain sequence reads, wherein an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA having the SNV locus is detected from the sequence reads.

'596 Patent at 172:9-14

At the Preliminary Injunction, Dr. Metzker Distinguished Finding a Mutation From Noise

Q. And why not?

* * *

A. Bentley is based on a different -- in a next-generation sequencing technology called 454, and 454 has a known error rate, just like other massively parallel sequencing systems, and the 454 system has an error rate of about 1 percent, and that's kind of how you can determine whether you can find your CT mutation. What's -- what level can you find your ctDNA is usually what the error rate is. If you're above the noise, you may find the signal; and if you're below the noise, you'll just mostly get noise.

Metzker Deposition (Preliminary Injunction Hearing, 11/27/2023) at 34:7, 34:13-21

During PI, Dr. Metzker Distinguished Forshew's Detection Based on Error Rates

1) Ultra-Deep Sequencing Does Not Enable Detection of Rare Genetic Variants that Fall Below the Sequencing Workflow Error Rate

Metzker Reply Decl ¶ 94

93. Specifically, the limitations of Forshew (2012)'s approach arise because the errors associated with Forshew (2012)'s sample library preparation and sequencing workflow exceed the technique's ability to detect rare genetic DNA variants, as explained in greater detail *infra*. Under the Forshew (2012) approach, the rare variants are lost in the "noise" associated with the abundant errors found in the sequence read data.

Metzker Reply Decl ¶ 93

Term B: "performing high-throughput sequencing of the amplified DNA comprising the plurality of target loci to obtain sequence reads, wherein an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA having the SNV locus is detected from the sequence reads"

NeoGenomics' Proposal	Natera's Proposal
Plain and ordinary meaning, no construction necessary beyond the constructions of Terms C and D below	Plain and ordinary meaning, which means that the terms are part of the "performing high-throughput sequencing . . . to obtain sequence reads" step and the "wherein" clause informs the mechanics of how the high-throughput sequencing is performed

Joint Claim Construction Chart, ECF No. 370-1 at 7-8

Sequencing and Detecting Can Occur On The Sequencer

"Processing steps to detect SNVs from sequence reads after obtaining the sequence reads could also be performed on the Illumina MiSeq instrument described in the '596 patent."

Opening Decl. of Dr. Lennon at ¶ 23

Court's Construction

"[T]he sequencing and detecting are all part of one sequencing step . . . the sequencing is done to detect SNVs, and the structure of the claim indicates that the detecting and sequencing are part of the same step."

Claim Construction Order, ECF No. 280 at 11